THE WILLIAM ALLAN MEMORIAL AWARD LECTURE

On the Nature of Men

JÉRÔME LEJEUNE[1]

To kill or not to kill, that is the question. [Unknown]

The correlation between chromosomal errors and their phenotypic consequences is sufficiently well established to allow us to decipher, however partially, the destiny of an individual just by looking at his chromosomes. For example, if we know that a subject will be developing from a fertilized egg carrying an extra chromosome 21, we know for sure that the individual will exhibit later all the characteristics of the 21-trisomy syndrome, including, among other abnormalities, severe mental deficiency. Hence the very practical point has been repeatedly advanced that if early detection of a chromosomal condition could be achieved (such as made possible by analysis of the cells floating in the amniotic fluid), a decision could be taken whether such a pregnancy would be allowed to go to term or would be interrupted by an induced abortion. Such a problem is so close to us and so obviously important that it has become one of the possible immediate consequences of recent advances in theoretical knowledge and technical capabilities. Without proposing to elaborate a new philosophy of the human condition, it seems appropriate that human geneticists realize that the question "to kill or not to kill," is by no means purely practical or technological. I will deliberately leave out of the discussion the ethical aspects, because I think human geneticists are no better qualified in ethics than are any other scientists. On the contrary, I would focus our attention on the biological aspects related to a mere observation: "What do we know about the time at which a new human being comes into existence?"

Such a query is not new, and here the geneticist is very similar to Diogenes coming out of his barrel and looking for a man. The only difference is that our lantern has been modernized into a microscope, and I would propose that we consider this quest for a man in the light of cytogenetical findings.

THE KARYOTYPE OF MANKIND

Our first statement is such a commonplace observation that we generally do not pay enough attention to it. All human beings now living on this planet share the

Presented on the occasion of receiving the William Allan Memorial Award at the meeting of the American Society of Human Genetics at San Francisco, October 2–4, 1969.

[1] Chaire de Génétique Fondamentale, Institut de Progénèse, 15, rue de l'École de Médecine, Paris-6e.

same karyotype. More precisely, apart from the XX and XY sexual dimorphism, every chromosomal pair is morphologically identical in all of us within the degree of uncertainty inherent in present methods. On the other hand, the continuous recurrence of "de novo" chromosomal rearrangements (like trisomies, monosomies, or various kinds of translocations) exemplifies the tremendous mutational pressure exerted upon the human karyotype. Furthermore, the heavy and painful tribute paid by each generation to meiotic or mitotic mistakes shows at what cost the constancy of the human karyotype is preserved.

If karyotypes other than the standard human chromosomal constitution were equally good or even better, human races should have split from each other, forming multiple karyotypic systems. This has not happened in our species although many examples can be found in other mammals. Conversely, fortuitous convergence of other karyotypic constitutions toward the human-type pattern becomes exceedingly improbable. We are then left with the interesting but academically uncomfortable conclusion that speciation in plants and animals is a very different process from human race formation, and we are obliged to use quotation marks when we speak about "Darwinian evolution of man."

No matter how we tackle the problem, it follows from the actual findings that the present-day human karyotype must have appeared first in an extremely small group, even as small as one couple, and must have maintained itself constant, simply because it was the very best solution. It follows also that mankind is a biological unit of which races are variations with no precise boundaries. Hence the old idea that human beings are brothers is not an ethical hypothesis or a purely moral goal, but simply a correct expression of plain reality. The recognition of such brotherhood is very comforting, but increases our concern as human geneticists for the destiny of those unfortunate children who do not share equitably our chromosomal heritage.

THE DISINHERITED CHILDREN

As we first noted, a question is thus raised: Should these variants of the human condition be allowed to live?

Here, to try to simplify the problem, we could first dismiss the problems raised by grown-up individuals or even newborns. No doubt exists, I suppose, that to suppress the life of an adult, an infant, or even a newborn, is to be classified as homicide, no matter how severely affected the patient should be.

Indeed it could be remarked that some conditions like 13 trisomy, for example, are not compatible with a prolonged extrauterine life. An argument could thus be presented that their suppression would be only equivalent to premature euthanasia. Without discussing the particular topic of euthanasia, a very strong difference must be stressed here: the purpose of euthanasia is to spare seemingly unnecessary suffering to *the patient*, while the goal of the suppression of a disabled child is to prevent suffering to *his family and to society.*

If we definitely are not concerned about the finished individual, what about the beginning of life? When the future human being is still a conglomerate of cells, apparently not yet differentiated, should we consider him as a human being or not? Should we reject this cell mass if it does not fit our specifications, or should we respect

him and protect him in all possible ways? Such a question, directly raised by the possible detection of a chromosomal error in a young embryo, has to be faced by human geneticists. Surely the answer must be based upon scientific grounds and be as free as possible from emotional or opportunistic reactions.

The necessity of assuming this duty is imperative. Geneticists cannot play Pontius Pilate and wash their hands, saying, "The parents will choose." Parents are generally not cytogeneticists, but are always deeply emotionally involved. How then could they judge?

THE TECHNICAL APPROACH

Challenged with this problem we can try a "technical" approach. Just for a moment let us suppose that the question of being a man or not is either irrelevant or already solved, and look for a "technical" solution. Although the matter seems, and indeed is, considerably simplified by such a bold statement, not all difficulties have vanished. We must first consider that the phenotypes determined by chromosomal aberrations cover an extremely broad spectrum.

At one extreme we can locate—apart from the 13 trisomy already mentioned—the 18 trisomy, the pure triploidies, and a few other conditions which are practically incompatible with prolonged extrauterine life. A second category includes severe conditions like trisomy 21 or Cri du Chat syndrome, which are entirely compatible with a long life expectancy but inflict severe physical impairments and a mental deficiency, although varying appreciably from subject to subject. In technical terms, we must stress that our predictions are quite accurate but are only negative. For example, the presence of an extra chromosome 21 in a fertilized egg gives us the following information: the children who will develop from this egg will never attend a high school and will not be able to live independently. Remarkably enough, we do not know whether the affected individual will be able to read, write, or count and achieve a mental age of seven or eight years, or whether he will have an extremely poor development, with an IQ below 20. Obviously the human geneticists looking at chromosomes have not yet reached the cleverness of the fairies who could predict everything just by looking at a baby in his cradle. However, our "misfortune-telling" is precise enough to know that the child will never be self-supporting in everyday life.

The other extreme of the spectrum is much more troublesome. For example, an XO woman, although sterile and slightly physically abnormal, can spend an interesting life found worthwhile by herself as well as by others. I have in mind the case of an excellent technician I met years ago in a laboratory of human biochemical genetics. The case of an XXY Klinefelter is still more ambiguous. Apart from sterility, a kind of built-in permanent contraception, an XXY subject can have a quite normal life and even can become a highly reputable surgeon—to cite another individual case.

Finally we find quite normal conditions, like triplo-X mothers, fortuitously detected, or XYY individuals who can enjoy a perfectly decent and respectable life. Indeed we know, statistically, that the XXX condition is far more frequent among inmates of institutions for mentally retarded persons, and we are quite convinced that the risk of delinquency is greater for an XYY man than for a "normal" XY

(although not greater than for an "abnormal" XY). But what about the condition of translocation carriers, not suffering any detectable genetic damage themselves but able to give birth to children suffering from an imbalanced karyotype? And what about complex translocations which, due to *aneusomie de recombinaison*, can occur in two different although morphologically identical karyotypes, one entirely balanced, leading to perfectly normal adults, the other severely imbalanced, and sometimes lethal or dramatically dysmorphogenic.

Intermingled with all the preceding cases is the cumbersome problem of mosaicism. Every human being is a mosaic due to some mitotic malsegregation in some part of the body; the dividing line between normal and pathologic is a matter of percentage: if 50% of abnormal karyotype is considered as deleterious, what about 40%, 20%, 5%, and what about topographical distributions? Obviously here some "technical" judgment has to be made about the human qualities resulting from a given constitution, and careful analysis of the burden imposed upon affected individuals, their families, and society must be made.

The burden to the individual himself is very difficult to assess because only the affected person can tell us about it. The overwhelming majority of patients suffering from a genetic disease (and able to express their feelings) do regret their affliction but do not regret being themselves and alive. The social burden possibly could be easier to estimate, but the suffering of the family will stay outside of any "technical" evaluation. Nevertheless, many precise but very complex questions must be solved. For example: is the Turnerian way of life to be accepted? is the 21-trisomic way of life to be protected? . . . , and the like. Willy-nilly we come to the conclusion that such a difficult matter, that of deciding what is desirable and should be respected and what is undesirable and should be rejected, deals with considerable "technical" intricacies. In such situations the common practice is not to leave the decision to unprepared or to directly involved persons, but to resort to some jurisdiction, or some body of counselors.

Thus the time is ripe to see what kind of facility for research and applied eugenics should be constituted to manage these problems. Indeed, there would be no reason whatsoever to limit the competence of this facility merely to chromosomal aberrations, but its terms of reference should include all inborn errors, either genic or chromosomal. In order to work out entirely this "technical" approach, let us read the minimal statutes that such a facility should have.

Elements of the Statutes of a New Facility for Research and Applied Eugenics

Article I

Considering the disputed issue of mankind's betterment, noting the burden imposed upon society by genic and chromosomal diseases, and recognizing the limitation of the available solutions, a special Institution for Research and Applied Eugenics is created: "THE NATIONAL INSTITUTE OF DEATH."

Article II

Under the scientific scrutiny of a board of specially appointed advisors, the NATIONAL INSTITUTE OF DEATH will:

A. Decree on undesirable genes or chromosomes.
B. Deliver unhappy parents from unwanted pregnancies.
C. Discard embryos not fitting standard requirements.
D. Dispose of newborns not reaching minimal specifications of normalcy.
E. And generally, destroy, delete, or decry any human condition voted against by the above-mentioned board of advisors of the NATIONAL INSTITUTE OF DEATH.

Article III

To prevent any possible error, concern, or prejudice, the advisors shall be chosen from among knowledgeable persons not belonging to any philosophy, society, or race.

THE INDIVIDUAL APPROACH

Leaving the board of advisors of the NATIONAL INSTITUTE OF DEATH to its intrinsic "technicalities," we have to remember that we have set aside the core of the problem: when does man begin? To make a short story long (for the beginning of life is just the brief instant of egg fertilization), we can investigate at what stage of development the future human being can be considered as an individual. The available information is spread over many fields of biology but can be summarized under the two headings defining an individual, that is, unity and uniqueness. It is actually impossible to state firmly at what time these two qualities appear, although we know for sure that it is after fertilization. But it is possible to delineate with the aid of pathological findings, the time *after which* these qualities cannot be appreciably changed.

Unity and Chimeras

According to the classical rules of human genetics, every individual is constructed out of one cell, the fertilized egg. This formal statement had no exception until the discovery of human chimeras in hermaphroditism. For example, in the constitution XX/XY, careful analysis of blood groups shows that the red cells are composed of two subpopulations, each of them carrying a particular array of genes coming from the parents. The primary mechanism of these chimeras is poorly understood but, broadly speaking, it can be asserted that two fraternal twin zygotes have collaborated to build together one embryo instead of two. Speculations about simultaneous fertilization of a reduced egg and of one of its polar bodies have been made, and diploid/triploid mosaics seem to owe their origin to a rather similar type of accident. Although other mechanisms could as well be postulated, the moment at which the process can occur is very early in development.

First, these events happen at the same ovulation period, for embryos a month apart could not fuse into one. Second, to realize the almost-perfect mixture of the two kinds of cells found in every tissue, the symbiosis must establish itself well ahead of the first general organization of the future embryo. This leaves us with a period of uncertainty not exceeding weeks and, quite likely, as short as a few days or hours if the polar body is involved. This problem of the unity of an individual of chimeric origin is intriguing. Compound animals can be artificially produced, like the mouse manufactured from blastocysts of different embryos, thus having many mothers and many

fathers. Such a monstrosity fortunately is not be be feared too much in our species, at least, as long as the good old manners of reproduction will be in use! Nevertheless, it seems likely that natural chimeras in our species are about twice as frequent as XX/XY hermaphrodites. The reason is that if two fraternal zygotes, both XX or both XY, fuse, the individual will be perfectly healthy and never examined. It is entirely possible that some here are not the pure clone they believe themselves to be, but are harmonious chimeras resulting from the full integration of two cellular races. Is it entirely chimerical to think that such a fruitful and peaceful coexistence between populations of cells, carrying different tables of the law of life, hopefully could be a model for human societies?

Uniqueness and Twins

The uniqueness of each man is also an old rule of genetics. Without developing any statistical demonstration, it can safely be assessed that the precise genetic constitution of every fertilized egg is unique, has never been realized before, and will never occur again. But at what moment is this uniqueness definitely established? Monozygous twins show that two or sometimes more individuals can emerge from the same primordial genetic information. Nobody, I venture, would seriously argue that identical twins are not individual persons although they share the very same nature. The splitting in two embryos surely can occur at the first cleavage of the egg, but what about the latest stage possible? The observation of double monsters demonstrates that complete separation cannot take place after the finalization of the neural crest. Hence, we are left again with an indeterminate period of assuredly less than one month and probably of two or three weeks at most.

Incidentally, again to break one of the old rules, twins coming from the same egg are not necessarily alike. If a chromosomal error intervenes during or just after cleavage, identical twins can be different. If a chromosome 21, for example, is present in triplicate in one twin and normally diploid in the other, the twin set will be composed of a typical 21-trisomic individual and of his normal co-twin, identical but for the 21 trisomy condition. If the accident prevents the transmission of the Y chromosome to one of the twins there will be one normal male (XY) and a female identical twin with Turner's syndrome (XO). In a case of this type, the XO girl apparently suffered from a very strange psychological disturbance which greatly intrigued the psychiatrists: she pretended she was seeing her brother when she looked at herself in a mirror. For the geneticist, such an intuitive knowledge of a complex situation was not at all troublesome, but a mere affirmation of the facts. But, coming back to our timing problem, in what way can all these remarks help us in answering our basic question: "when does a human being begin?"

THE MOLECULAR APPROACH

During the transmission of life, the link between parents and infants is continuous. Without reviewing the complex machinery of coded molecules, from DNA and RNA to ribosomes and proteins, we can safely assume that at every moment this link between generations is material. Nevertheless, with exactly the same degree of certainty, we know that no one molecule, no one individual atom actually present in

the fertilized egg, will have the slightest chance of being transmitted to the next generation. Obviously what is "transmitted" is a form, an accident of the matter, and not matter itself as such. This apparent paradox is the very basis of any reproductive process. For example a statue cannot be built out of void; it needs a material substrate such as marble or clay. During reproduction by molding, the link between the statue and its replicate is at every instant a material one; but what *is* reproduced is definitely not the marble or the plaster but the form, or, more precisely, the information imprinted on matter by the genius of the sculptor.

Applied to biology, this principle of information transfer is perfectly relevant because we know that, if not disturbed and if not deprived of nutrient supply, the fertilized egg on its own will produce a full-blown individual by an extremely complex but entirely deterministic mechanism. In utero relations between the mother and the fetus do not affect at all this fundamental determinism, as is clearly demonstrated by the egg of the hen. By such reasoning, the information specialist reaches the conclusion that the more deterministic and materialistic his conception of life, the earlier a human constitution is entirely spelled out. If man is considered as an accretion of matter such that his very nature is entirely dictated by the information imprinted in these materials, then a new man begins at the precise point the necessary and sufficient information is gathered, that is, at the very beginning.

Even interpretation of his theory in philosophical terms will not lead the information specialist any further. Indeed, it could be argued that all nuclear and cytoplasmic information included in the fertilized egg is only describing the "essence" of the future man, not his "existence." But this reserve vanishes immediately if we accept the fact that existence is essence in action. Hence since any transmission of information is the action of its essence, the future man effectively exists either at the first RNA synthesis or, if we need a more ostensible starting point, at the first cell cleavage. Whether or not we find that reducing man to the genetic and organistic information of his primordial cell is intuitively satisfactory, no clear direction seems open to pursue the argument.

THE PRACTICAL APPROACH

Many would consider that we have spent enough time on pure and unproductive speculations and would stop here, saying, "Wait, let us be practical and see the mere facts."

At the early stages of embryonic development there are only conglomerated cells, rapidly dividing. This little mass even does not look at all like a man; it is just a piece of flesh, a very precious flesh because a human being could sprout out of it—a fact impossible from an ordinary tissue culture or from any somatic part of the body. But there is no "humanity" there, just human cells. In this approach, different landmarks can be used in deciding that "humanity" has been acquired by the "thing." Some will hold that organs must have differentiated; others will require some development of the brain; and others will wait until certain reactions to stimuli occur in the fetus or until any other specified step is attained. It follows that the time factor we are interested in varies largely with this approach, for example from fertilization to viability, or, when the disputation is entirely worked out, to the time at which the

"growing thing" will finally be able to pretend that he is a man. Generally the process of birth is accepted as a convenient term for the discussion, but this separation from the mother is not relevant whatsoever to the logic of the argument.

When viewed scientifically, this difficulty in spelling out "practically" at what precise time a mass of cells becomes a man is not surprising at all and definitely is not to be ridiculed. If we dissect the intellectual pathway followed here, it is clear that regardless of the circumlocutions used, what the "practical" view is looking for is in plain words: is there some kind of human "soul" or not? Ensoulment theory has been vividly discussed by theologians but, to the best of my knowledge, never solved. Thus, it is no wonder that "practical" discussants cannot beat specialists on their own ground. Curiously enough, we have seen the "molecular theoretician" coming out with a pure information theory, very akin to physical representation of the "incarnation of the logos" and the "pragmatist" discussing the first symptoms of the existence of the "human soul." It could very well be that such an apparent confusion of disciplines stems from the fact that we all tried to solve an incomplete problem.

For the sake of simplification, we have devoted ourselves to the particular query: "When does man begin?" It appeared to be quite a clear-cut question. But should we not have been better inspired to start with the necessary question: "What is a man?" No dictionary and even no legislation of any country or civilization has ever fully answered this question. Depending upon what different specialists look for in man—his quality, his individuality, his molecules, or his internal or external life—the "technician," the "personalist," the "information specialist," and the "pragmatist" have given their own answers not to the question we asked them, "When does man begin?" but to the unspelled challenge, "What is a man?" Certainly this is the crux of the matter, but such a crux is possibly too heavy to be carried by a human mind.

Here are we left, exactly at the same point we started two thousand years ago. The Diogenes-geneticist returns to his barrel after turning off his microscopic lantern. He has not discovered when and where man could be found! Conclusions from such a circular trip are not straightforward! Nevertheless we human geneticists have to face everyday reality: disabled children and distressed parents exist. No formal demonstration being at hand, each of us has to face the challenge, and I believe our response must be guided by two sentiments only—humility and compassion. Humility because we must recognize we have no ready-made answers, because geneticists have not broken the secret of the human condition, and because scientific arguments are of little help in ethical issues; compassion because even the most disinherited belongs to our kin, because these victims are poorer than the poorest, and because the sorrow of the parents cannot be consoled by science. But should we capitulate in the face of our own ignorance and propose to eliminate those we cannot help?

For millennia, medicine has striven to fight for life and health and against disease and death. Any reversal of the order of these terms of reference would entirely change medicine itself. It happens that nature does condemn. Our duty has always been not to inflict the sentence but to try to commute the pain. In any foreseeable genetical trial I do not know enough to judge, but I feel enough to advocate.